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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/403,882	03/20/2000	JAVIER FARINAS	UCSF1100-3	7814

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 01/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/403,882	FARINAS, JAVIER	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,8-18,60,64,65,75 and 77-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-2, 8-18, 60, 64-65, 75, and 78-80* is/are allowed.

6)☒ Claim(s) *77 and 81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/20/00* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/2/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/28/04 has been entered.

2. Claims 1-2, 8-18, 60, 64-65, 75, and 77-81 are pending and are being acted upon in this Office Action.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 77 and 81 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for localizing a probe within a cell as set forth in claims 1-2, 8-18, 60, 64-65, 75, and 78-80, (2) a method for localizing a probe within a cell wherein the single chain antibody comprises the amino acid sequence set forth in SEQ ID NO: 2 or an amino acid sequence encoded by the nucleic acid sequence set forth in SEQ IDNO: 1, **does not** reasonably provide enablement for a method for localizing a probe within a cell wherein the single chain antibody comprises (1) the amino acid sequence set forth in SEQ ID NO: 2 "with up to 30 conservative amino acid substitutions"; (2) any amino acid sequence at least "95% identical to SEQ ID NO: 2"; (3) any amino acid sequence encoded by any nucleic acid sequence at least "95% identical to SEQ ID NO: 1". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable

one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only one single chain antibody that binds specifically to phOx which encoded by a polynucleotide comprising SEQ ID NO: 1. The specification further discloses a method of for localizing a probe within a cell comprising contacting a sample comprising a cell transfected with the polynucleotide of SEQ ID NO: 1 that encodes a single chain antibody that binds specifically to PhOx ligand with a membrane permeant probe Biody Fl conjugated to the ligand PhOx. The probe moiety is coupled to the ligand PhOx via a flexible aliphatic linker such as diaminopetane. The method further comprises the step of adding a stimulus to the cell and detecting said probe/ligand conjugate, before and after addition of the stimulus.

The specification does not teach how to make any single chain antibody comprises the amino acid sequence such as (1) SEQ ID NO: 2 "with up to 30 conservative amino acid substitutions"; (2) any amino acid sequence at least "95% identical to SEQ ID NO: 2"; (3) any amino acid sequence encoded by any nucleic acid sequence at least "95% identical to SEQ ID NO: 1" for the claimed method because of the lack of structure of said single chain antibody without the amino acid sequence, the corresponding nucleic acid sequence. There is insufficient guidance as to which 30 amino acids within the full length sequence of SEQ ID NO: 2 that comprises 316 amino acids to be substitute and whether the resulting single chain antibody maintains its binding specificity to phOx ligand. A 95% sequence identity to SEQ ID NO: 2 means at least 5% difference, which is equivalent to approximately 16 amino acids substitution, deletion, addition and combination thereof. There is insufficient guidance as to which amino acids within the full length sequence of SEQ ID NO: 2 to be substitute for which amino acid, which amino acids to be deleted or added and whether the resulting single chain antibody maintains its binding specificity. There is inadequate working examples demonstrating that any modification to SEQ ID NO: 2 still binds to phOx for the claimed method. Likewise, a nucleic acid sequence at least 95% identical to SEQ ID NO: 1 is equivalent to 78 nucleotides differences. There is a lack of guidance as to which nucleotides within SEQ ID NO: 1 to be added, deleted, substituted and combination thereof and whether the resulting polynucleotide still encodes a single chain antibody that binds specifically to phOx for the claimed method.

The use of "percent" in conjunction with *any* of the various terms that refer to sequence identity or similarity is a problem because sequence identity between two sequences has no common meaning within the art. The term "percent" is relative and can be defined by the algorithm and parameter values set when using the algorithm used to compare the sequences. The scoring of gaps when comparing one sequence to another introduces uncertainty as to the percent of similarity between two sequences.

Skolnick *et al,* or record, teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Abaza *et al*, of record, teach even a single amino acid substitution outside of an antigenic site on protein can exert drastic efefcts on the binding specificity of the monoclonal antibody (See entire document, abstract, in particular).

Winkler *et al* teach single amino acid substitution in an antibody binding region can change the specific binding of a certain functional epitope by two orders of magnitude or even more (see page 4513, col. 2, in particular) and substantial changes to antibody binding specificity can be observed by single amino acid exchanges (see entire document, abstract, in particular).

Given the lack of guidance as to which specific nucleotide within SEQ ID NO: 1, the corresponding amino acid residues within the full length sequence of SEQ ID NO: 2 can be substituted, deleted, and combination thereof, it is unpredictable which single chain antibody comprising an undisclosed polypeptide with no more than 30 amino acid substitution encoded by the undisclosed polynucleotide would maintain its binding specificity to phOx, in turn, useful for the claimed method.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

Applicants' arguments filed 10/28/04 have been fully considered but are not found persuasive.

Applicants' position is that Claims 1 and 60 have been amended to recite a ligand comprising phOx. It would be a matter of routine experimentation, not undue experimentation, for one skilled in the art to identify a single chain antibody that specifically binds to phOx and an amino acid sequence different from SEQ ID NO: 2. Exhibit A (Bowie et al Science 247 : 1305) teaches that proteins are surprisingly tolerance of amino acid substitutions.

In response, Bowie et al reference is irrelevant to the claimed method because the reference discloses prokaryote lac repressor. The claimed invention is drawn to a method for localizing a probe within a cell by expressing a single chain antibody that binds specifically to phOx. As evident by the teachings of Winkler *et al* that a single amino acid substitution in single chain antibody binding region can change the specific binding of a certain functional epitope by two orders of magnitude or even more (see page 4513, col. 2, in particular) and substantial changes to antibody binding specificity can be observed by single amino acid exchanges (see entire document, abstract, in particular). Let alone a nucleic acid sequence encoding a polypeptide consisting of the amino acid seuqence set forth in SEQ ID NO: 2 with up to 30 conservative amino acid substitutions, or at least 95% identical to SEQ ID NO: 2.

The specification discloses only one single chain antibody that binds specifically to phOx which encoded by a polynucleotide comprising SEQ ID NO: 1. The specification further discloses a method of for localizing a probe within a cell comprising contacting a sample comprising a cell transfected with the polynucleotide of SEQ ID NO: 1 that encodes a single chain antibody that binds specifically to PhOx ligand with a membrane permeant probe Biody Fl conjugated to the ligand PhOx. The probe moiety is coupled to the ligand PhOx via a flexible aliphatic linker such as diaminopetane. The method further comprises the step of adding a stimulus to the cell and detecting said probe/ligand conjugate, before and after addition of the stimulus.

The specification does not teach how to make any single chain antibody comprises the amino acid sequence such as (1) SEQ ID NO: 2 "with up to 30 conservative amino acid substitutions"; (2) any amino acid sequence at least "95% identical to SEQ ID NO: 2"; (3) any amino acid sequence encoded by any nucleic acid sequence at least "95% identical to SEQ ID NO: 1" for the claimed method because of the lack of structure of said single chain antibody without the amino acid sequence, the corresponding nucleic acid sequence. There is insufficient guidance as to which 30 amino acids within the full length sequence of SEQ ID NO: 2 that comprises 316 amino acids to be substitute and whether the resulting single chain antibody

maintains its binding specificity to phOx ligand. A 95% sequence identity to SEQ ID NO: 2 means at least 5% difference, which is equivalent to approximately 16 amino acids substitution, deletion, addition and combination thereof. There is insufficient guidance as to which amino acids within the full length sequence of SEQ ID NO: 2 to be substitute for which amino acid, which amino acids to be deleted or added and whether the resulting single chain antibody maintains its binding specificity. There is inadequate working examples demonstrating that any modification to SEQ ID NO: 2 still binds to phOx for the claimed method. Likewise, a nucleic acid sequence at least 95% identical to SEQ ID NO: 1 is equivalent to 78 nucleotides differences. There is a lack of guidance as to which nucleotides within SEQ ID NO: 1 to be added, deleted, substituted and combination thereof and whether the resulting polynucleotide still encodes a single chain antibody that binds specifically to phOx for the claimed method.

5. Claims 77 and 81 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of all single chain antibody comprises (1) any the amino acid sequence set forth in SEQ ID NO: 2 "with up to 30 conservative amino acid substitutions"; (2) any amino acid sequence at least "95% identical to SEQ ID NO: 2"; (3) any amino acid sequence encoded by any "nucleic acid sequence at least 95% identical to SEQ ID NO: 1" for the claimed method of localizing a probe within the cell.

The specification discloses only one single chain antibody that binds specifically to phOx which encoded by a polynucleotide comprising SEQ ID NO: 1. The specification further discloses a method of for localizing a probe within a cell comprising contacting a sample comprising a cell transfected with the polynucleotide of SEQ ID NO: 1 that encodes a single chain antibody that binds specifically to PhOx ligand with a membrane permeant probe Biody Fl conjugated to the ligand PhOx. The probe moiety is coupled to the ligand PhOx via a flexible aliphatic linker such as diaminopetane. The method further comprises the step of adding a stimulus to the cell and detecting said probe/ligand conjugate, before and after addition of the stimulus.

Besides the specific polynucleotide of SEQ ID NO: 1 that encodes for a single chain antibody that binds specifically to phOx for a method for localizing a probe within the cell, there

is insufficient **written description** about the structure associated with function without the polynucleotide sequence of the *other* single chain antibody such as single chain comprises the amino acid sequence set forth in "SEQ ID NO: 2 with up to 30 conservative amino acid substitutions without the amino acid sequence". There is inadequate written description about which 30 amino acids within the full length amino acid sequence of SEQ ID NO: 2 to be substitute for which amino acids, let alone the single chain antibody still binds to phOx. Likewise, a 95% sequence identity to SEQ ID NO: 2 means at least 5% difference, which is equivalent to approximately 16 amino acids substitution, deletion, addition and combination thereof. There is insufficient written about which amino acids within the full length sequence of SEQ ID NO: 2 to be substitute for which amino acid, which amino acids to be deleted or added without the amino acid sequence. Along the same line of reasoning, there is inadequate written description about the nucleotides within SEQ ID NO: 1 to be added, deleted, substituted and combination thereof and whether the resulting polynucleotide still encodes a single chain antibody that binds specifically to phOx for the claimed method without the nucleotide sequence.

Further, the specification discloses only *one* single chain antibody that binds specifically to PhOx for the claimed method. Given the lack of a written description of *any* additional representative species of polypeptide and polynucleotide encoding other single chain antibody that binds to phOx for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 10/28/04 have been fully considered but are not found persuasive.

Applicants' position is that claims 1 and 60 have been amended. While the law does not require that the specification describe every species within the genus.

In response, the specification discloses only one single chain antibody that binds specifically to phOx which encoded by a polynucleotide comprising SEQ ID NO: 1. The specification further discloses a method of for localizing a probe within a cell comprising

contacting a sample comprising a cell transfected with the polynucleotide of SEQ ID NO: 1 that encodes a single chain antibody that binds specifically to PhOx ligand with a membrane permeant probe Biody Fl conjugated to the ligand PhOx. The probe moiety is coupled to the ligand PhOx via a flexible aliphatic linker such as diaminopetane. The method further comprises the step of adding a stimulus to the cell and detecting said probe/ligand conjugate, before and after addition of the stimulus.

Besides the specific polynucleotide of SEQ ID NO: 1 that encodes for a single chain antibody that binds specifically to phOx for a method for localizing a probe within the cell, there is insufficient **written description** about the structure associated with function without the polynucleotide sequence of *other* single chain antibody such as single chain comprises the amino acid sequence set forth in SEQ ID NO: 2 with up to 30 conservative amino acid substitutions without the amino acid sequence. There is inadequate written description about which 30 amino acids within the full length amino acid sequence of SEQ ID NO: 2 to be substitute for which amino acids and whether the resulting single chain antibody still binds to phOx. Likewise, a 95% sequence identity to SEQ ID NO: 2 means at least 5% difference, which is equivalent to approximately 16 amino acids substitution, deletion, addition and combination thereof. There is insufficient written about which amino acids within the full length sequence of SEQ ID NO: 2 to be substitute for which amino acid, which amino acids to be deleted or added without the amino acid sequence. Along the same line of reasoning, there is inadequate written description about the nucleotides within SEQ ID NO: 1 to be added, deleted, substituted and combination thereof and whether the resulting polynucleotide still encodes a single chain antibody that binds specifically to phOx for the claimed method without the nucleotide sequence.

Further, the specification discloses only one single chain antibody that binds specifically to PhOx for the claimed method. Given the one and only single chain antibody that binds to phOx and the lack of a written description of *any* additional representative species of polypeptide and polynucleotide encoding other single chain antibody that binds to phOx for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. Claims 77 and 81 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "up to 30 conservative amino acid substitutions" in claims 77 (b) and 81(c), the "at least 95% identical to SEQ ID NO: 2" in claims 77 (c) and 81(d), and "at least 95% identical to SEQ ID NO: 1" in claims 77(e) and 81(b) represent a departure from the specification and the claims as originally filed. The passages pointed out by applicant in the amendment filed 10/28/04 do not provide a clear support for the said phrases.

7. Claims 1-2, 8-18, 60, 64-65, 75, and 78-80 are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

9. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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January 7, 2005

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